THE JOURNAL OF INVESTIGATIVE DERMATOLOGY, 69:198–204, 1977

Vol. 69, No. 2
Printed in U.S.A.

A DEVELOPMENTAL STUDY OF THE DISTRIBUTION AND FREQUENCY OF LANGERHANS CELLS IN RELATION TO FORMATION OF PATTERNING IN MOUSE TAIL EPIDERMIS

JÜRGEN SCHWEIZER, PH.D., AND FRIEDRICH MARKS, PH.D.

German Cancer Research Center, Institute of Biochemistry, Heidelberg, Germany

The structure of mouse tail epidermis has been investigated from day 15 of embryonic development and a qualitative and quantitative analysis of the localization of Langerhans cells has been carried out using the ATPase method.

Langerhans cells occur exclusively in regions where a granular layer is present in the developing epidermis. The appearance of both a granular layer and evenly distributed Langerhans cells is noted for the first time at embryonic days 16 to 17. At postnatal day 3 the number of Langerhans cells as well as the thickness of the granular layer are increased although the characteristic scale–interscale pattern of adult mouse tail skin is not yet outlined. This occurs first around postnatal day 9 and is characterized by a gradual reduction of the granular layer in the regions surrounding the forming scales. Exactly the same areas are occupied by Langerhans cells.

This pattern of distribution is maintained in the adult animal. Repeated treatment of adult mouse tail skin with vitamin A results in a conversion of the para-keratotic epidermis into an ortho-keratinizing one, so that a granular layer is present throughout the whole epidermis. Concomitantly, Langerhans cells can clearly be demonstrated in the scale regions.

Considerable variations in the morphologic appearance and properties of epithelial tissues are common features in mammals. In the tail epidermis of rodents this situation is carried to extremes in that in areas extremely close to each other, two completely different structures are encountered [1–3]. The mouse tail epidermis is made up of a regular system of slightly elevated scales arranged in rings around the long axis. In the small regions between the rings, groups of hairs emerge under each scale [1,4,5]. Adjacent scale rings are out of phase so that interscale regions of one ring are opposite the midscale regions of the adjacent rings. Vertical sections of adult mouse tail skin reveal that the epidermis under the scales keratinizes in a para-keratotic manner resembling in many aspects psoriatic epidermis [2,6,7], whereas the epidermis between adjacent rings and lateral to each scale forms a granular layer together with a flaky, loosely packed cornified layer (see Fig. 9). The transitional zones between the two epidermal structures are unusually sharp and can be followed easily with the light microscope [2].

The aim of the present investigation was to study the development of these special structures of tail epidermis of the mouse from the embryonic to the adult stage. A concomitant study concerning the localization of Langerhans cells in the developing tail epidermis was undertaken. To demonstrate Langerhans cells at the light-microscopic level, the ATPase staining method [8] was chosen. The application of this method allows, if certain criteria are respected [9,10], the identification of Langerhans cells with a high degree of confidence. Investigations in the past years have adequately demonstrated that the high-level, dendritic Langerhans cells constitute an active, intraepidermal cell population, capable of division [11,12] and not related to the pigmentary system [8,9,13]. There is some evidence indicating that Langerhans cells are mesenchymal in origin [13, 14], but despite the accumulation of numerous experimental data their function and biologic significance are still unknown. One proposal assumes that Langerhans cells might be involved in epidermal growth control in that they may produce chalone-like inhibitors of cell proliferation [15]. Since the chalone mechanism is closely related to the morphology and the state of differentiation of the epidermis [16], it was hoped that the distribution and frequency of Langerhans cells in relation to the developing patterning in tail epidermis could provide some information in favor or against this idea.

Manuscript received December 20, 1976; accepted for publication February 24, 1977.

Reprint requests to: Dr. J. Schweizer, German Cancer Research Center, Institute of Biochemistry, Im Neuenheimer Feld 280, 6900 Heidelberg, Germany.

MATERIALS AND METHODS

NMRI mice, kept under an artificial day–night rhythm (light phase from 12:00 to 24:00) were used in all experiments. Embryonic mice of defined stage of devel-

opment were obtained after a 1-day mating period of parent animals. Day of mating was counted as day 0. The designation "postnatal mice" refers to animals born 21 days post mating. The tails of the mice, varying in age from day 15 of embryonic development to 7 weeks after birth, were cut off; a longitudinal cut was made by means of a scalpel or scissors, and the tail skin stripped off from cartilage and bone. Except for the embryonic and day-3 postnatal mice, the tails were routinely depilated with Pilca cream (Olivin, Wiesbaden) prior to dissection.

Hematoxylin staining of epidermal sheets. Tail skin was kept overnight at 4°C in 1% acetic acid and the epidermis separated from dermis by means of forceps. Epidermal sheets were rinsed briefly in distilled water and stained free-floating in hematoxylin. Sheets from embryonic and neonatal mice required 5 min, and sheets from adult mice 8 to 10 min, for optimal staining. After differentiation in weakly acidic 70% ethanol, sheets were rinsed in distilled water, kept in tap water for 20 min, and mounted flat in glycerin jelly.

ATPase staining of epidermal sheets. Tail skin was incubated at 37°C in buffered 20 mM EDTA [17]. After 1.5 to 2 hr of incubation the epidermis could readily be separated from dermis with fine forceps. The epidermal sheets were stained for ATPase activity according to a modified Wachstein and Meisel method [18], described by Mackenzie and Squier [10]. Stained specimens were mounted in glycerin jelly.

ATPase staining of vertical sections (I. C. Mackenzie, personal communication). Flattened pieces of whole tail skin were fixed in the following fixative. Four grams of paraformaldehyde were dissolved by gently heating on a water bath (60–70°C) in 20 ml of double-distilled water to which 3–5 drops of 0.1 N NaOH had been added. Eighty milliliters of 0.1 M Na-cacodylate and 6.84 gm sucrose were added and the pH adjusted to 7.35. Fixation time was 4 hr. Pieces were rinsed briefly in double-distilled water and embedded vertically in small pieces of fresh mouse liver. Samples were quickly frozen and prepared for freeze sectioning. Skin sections, 15 μ in thickness, were cut and stored at −20°C until required. Staining procedure was similar to that described for epidermal sheets [10].

Treatment with vitamin A acid. The vitamin A preparation used was a suspension of vitamin A acid (Serva, Heidelberg; 300,000 IU/100 mg vitamin) in a mixture containing 20% propylenyglycol, 10% Tween 20, 30% glycerin, and 40% water, thus resembling the "Aquasol" employed by Lawrence and Bern [19]. The concentration of the suspended vitamin was 200 IU per 50 μl of the mixture. The suspension was stored at 4°C; 1 hr prior to application it was vigorously stirred.

A group of 10 female mice, 7 weeks old, received 50 μl of the suspension (200 IU = 60 μg of vitamin) applied daily for 15 days to an area of about 3 cm^2 of tail epidermis 1 cm caudal to the termination of the dorsal pelage. Ten control animals received 50 μl of the vitamin A-free solvent mixture per day and animal.

Histologic procedures. Five-micron sections of all samples of tail skin investigated were stained routinely with hematoxylin and eosin. Epidermal thickness and size of tail scale regions were measured under a microscope with a calibrated eyepiece reticule. In epidermal sheets, the ATPase-positive cells were counted by means of the same reticule at a magnification of 200. One field outlined by the reticule corresponded to an area of 0.276 mm^2. Cells were counted in 10 to 20 fields and the cell population was expressed as numbers of cells per mm^2 of epidermal surface.

RESULTS

Fifteen-day embryonic mice. Vertical sections of tail skin (Fig. 1) show a periderm-containing epidermis with a layer of columnar basal cells and 3 to 4 layers of cells with roughly spherical nuclei in the intermediate layers [20]. Neither hematoxylin nor ATPase staining of epidermal sheets revealed any structural organization.

Sixteen- to seventeen-day embryonic mice. At this stage of development epidermis is thickest (Tab.). Periderm has been largely lost. For the first time in embryonic development, a discrimination between basal, spinous, granular, and cornified layers can be made (Fig. 2). There are 2 to 3 layers of cells forming the stratum granulosum and the stratum corneum is still extremely thin [20]. No distinct structural organization appears upon hematoxylin staining of epidermal sheets. However, staining for ATPase activity in whole mounts clearly demonstrates dendritic cells, sparsely scattered throughout the epidermis (Fig. 3). Their frequency is about 100 cells per mm^2 (Tab.).

Three-day postnatal mice. The epidermis is composed of 6 to 7 layers of living cells, 3 to 4 of which can be attributed to the pronounced granular layer (Fig. 4). The transitional region between the granular and the cornified layer shows slight depressions, regularly spaced at distances of about 100 μ. Keratohyaline granules are especially abundant in the vicinity of these structures.

Developing hair follicles are arranged in parallel rows of groups of 3 hairs, the central follicle being generally most developed. ATPase staining of epidermal sheets (Fig. 5) reveals a regularly spaced population of dendritic cells, with a density of about 400 to 500 cells per mm^2 (Tab.). The ATPase enzymatic reaction is equally intense in all of the dendritic cells and no regional difference is seen in their distribution and size or complexity of their dendrites. Dendritic cells are positioned above the basal layer. No dendritic cells can be seen in the developing hair follicles.

Nine-day postnatal mice. Although there is almost no reduction in epidermal thickness (Tab.),

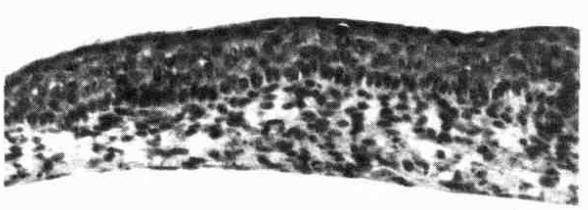

FIG. 1. Vertical section of tail skin of 15-day embryonic mouse (H & E; × 240).

TABLE. *Parameters determined in growing tail epidermis*

Day	Thickness of tail epidermis (μ)[a]	Width of scale rings (μ)[a]	No. of Langerhans cells per mm² of epidermis[b]
−6	40.29 ± 4.32[c]		–
−4	49.49 ± 14.20		111.96 ± 19.64
1	46.70 ± 6.51	74.26 ± 6.62[e]	not determined
3	47.23 ± 12.63	97.06 ± 0.74[e]	437.32 ± 34.89
9	47.99 ± 9.47[d]	167.68 ± 2.94	836.96 ± 48.73
15	34.62 ± 5.33[d]	264.70 ± 31.62	not measurable[f]
49	39.35 ± 2.66[d]	501.85 ± 44.44	not measurable[f]
210	–	601.81 ± 44.44	–

[a] Values reported represent the mean value of 20 measurements (4 sections; 5 measurements per section).
[b] See *Materials and Methods*.
[c] Plus periderm.
[d] Determined in midscale region from the basal layer to the underside of the stratum corneum.
[e] Formation of scales is not yet visible within the epidermis itself; data indicated represent distances between follicular rows.
[f] See *Results*: *Fifteen-day postnatal mice*; *Seven-week postnatal mice*.

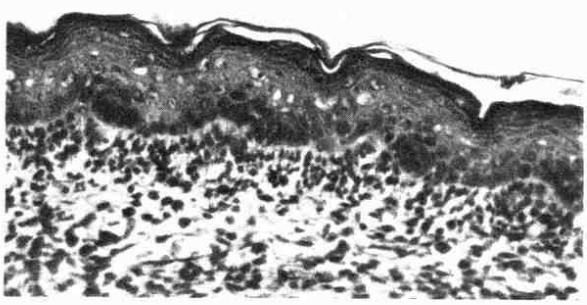

FIG. 2. Vertical section of tail skin of 17-day embryonic mouse (H & E; × 240).

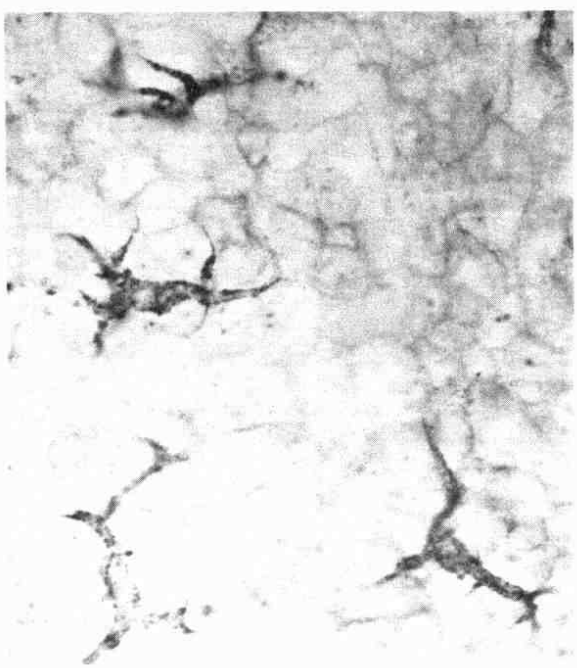

FIG. 3. Langerhans cells in EDTA-separated sheet of 16-day embryonic mouse tail epidermis (ATPase staining; × 450).

the slight depressions seen at day 3 have obviously extended and the scale and interscale regions are now clearly visible. There is still a continuous band of granular layer throughout the whole epidermis, although occasionally the granular layer seems to be reduced in some scale regions (Fig. 6). Parallel rows about 170 μ in width (Tab.) indicate the extent of the growing scale rings. The central hair follicle has developed a hair emerging through the epidermis; the lateral follicles are comparable in size with the central follicle at day 3.

In contrast to the situation of day 3, most of the ATPase-positive cells are concentrated at the distal parts of the developing scale ring systems whereas the proximal parts as well as the centers of the rings contain fewer cells, which exhibit a strong reduction of their dendritic processes and are almost round in shape (Fig. 7). The number of dendritic cells per mm² has increased to 800 to 900 (Tab.).

Fifteen-day postnatal mice. The formation of scale and interscale regions has further advanced (not shown). The granular layer is now confined to the ortho-keratotic interscale regions whereas in the para-keratotic scale regions the granular layer has disappeared. When compared with day 9, epidermal thickness is reduced (Tab.) and no longer uniform, the scale epidermis being significantly thicker than the interscale epidermis. The parallel scale rings appear in 270-μ intervals (Tab.). The interscale regions are deeply stained by hematoxylin, whereas in the center of the scales staining is only faint. Differences in hair size are no longer visible.

Dendritic cells are concentrated around the scale structures, the center of the scales is almost free of dendritic cells (Fig. 8). Due to this uneven distribution, data indicating frequency per mm² of epidermis can no longer be given. However, it is obvious that a considerable drop in the overall frequency of dendritic cells has occurred.

Seven-week old mice. The boundary lines between the two epidermal zones are now extremely clear-cut. The granular layer is strictly confined to the imbrications behind the scales and the lateral boundaries of scales within one ring. Its cessation is abrupt and can be followed up to the horny layer where a clear difference in the staining intensity of the para- and ortho-keratin is visible (Fig. 9). Width of the parallel scale rings is now about 500 μ and does not change significantly in older animals (Tab.).

Dendritic cells are absolutely restricted to the regions underneath the zones of ortho-keratinization (Fig. 10). When the frequency of Langerhans cells is determined per interscale region (without being referred to mm^2 of epidermis) the mean value is about 40 to 45 cells in both 15-day and 7-week-old animals. For the first time, dendritic cells appear in the necks of hair follicles [21].

Vitamin A acid-treated adult mice. Daily application of vitamin A over a period of 15 days produced a pronounced hyperplasia in the tail epidermis, which was absent from the control mice treated only with the solvent mixture. The most striking feature in the vitamin-treated epidermis is the introduction of a granular layer (Fig. 11) and the appearance of ATPase-positive dendritic cells in the scale region (Fig. 12). Furthermore, in hematoxylin and eosin-stained sections, no difference in the staining intensity of the entire horny layer can be seen (compare Figs. 9 and 11), although the stratum corneum of the scale epidermis does not generally correspond to the flaky type of keratin in the interscale regions. This conversion of the para-keratotic scale epidermis into an ortho-keratotic one together with the occurrence of ATPase-positive cells in the scale regions was evident in 8 of 10 animals.

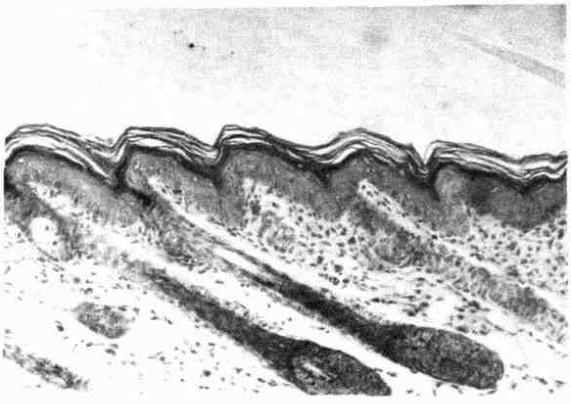

FIG. 6. Vertical section of tail skin of 9-day-old mouse (H & E; × 120).

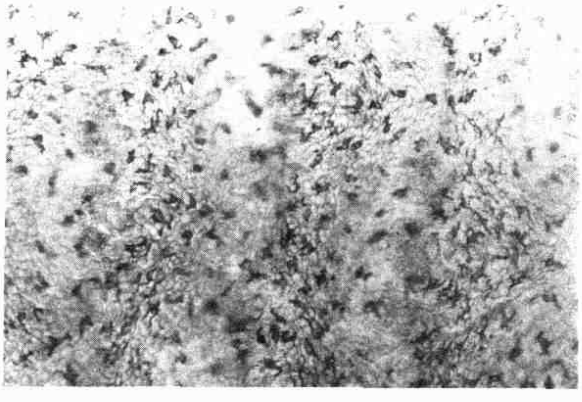

FIG. 7. Langerhans cells in EDTA-separated sheet of 9-day-old mouse tail epidermis (depilated) (ATPase staining, × 110). Figures 7, 8, and 12 are slightly out of focus. This is due to the fact that sheets of the strongly undulated epidermis can be mounted only under slight pressure, otherwise heavy deformations of the material occur. The variable thickness of the mounts does not allow sharp focusing in cases where Langerhans cells occur in scale as well as in interscale regions. In contrast, Langerhans cells can be focused in mounts where they are situated exclusively in one region (see Fig. 10).

FIG. 4. Vertical section of tail skin of 3-day-old mouse (H & E; × 230).

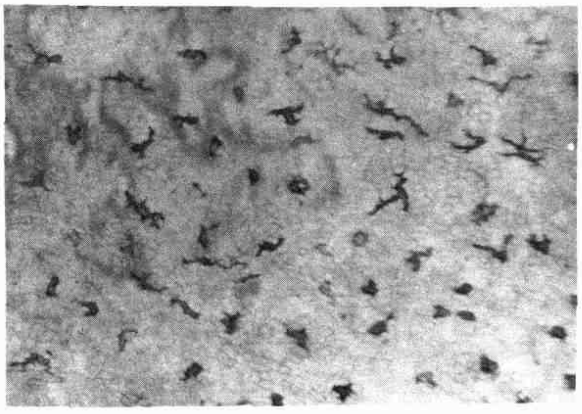

FIG. 5. Langerhans cells in EDTA-separated sheet of 3-day-old mouse tail epidermis (ATPase staining; × 120).

DISCUSSION

In the course of a developmental study of the formation of the scale–interscale patterning in mouse tail epidermis, strongly ATPase-positive dendritic cells localized in the upper part of the epidermis could be demonstrated. These cells exhibit two of the characteristics normally attributed to Langerhans cells [13]. A striking coincidence and local conformity of Langerhans cells

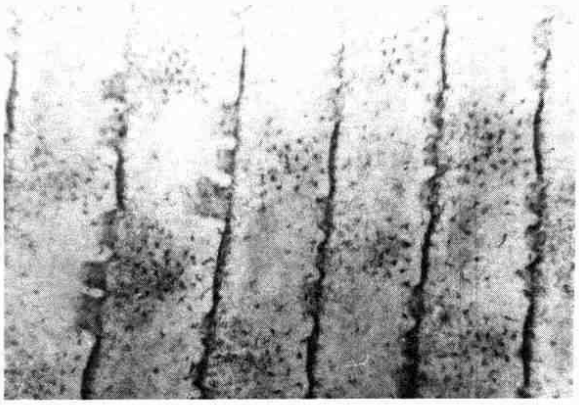

FIG. 8. Langerhans cells in EDTA-separated sheet of 15-day-old mouse tail epidermis (depilated) (ATPase staining; × 50).

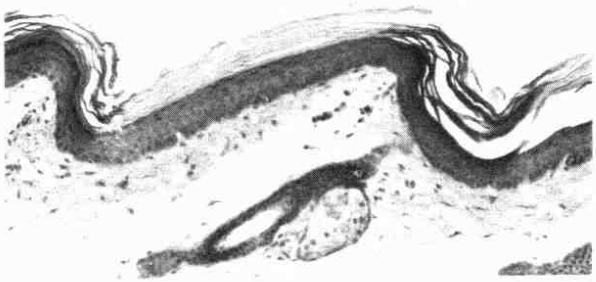

FIG. 9. Vertical section of tail skin of 7-week-old mouse (H & E; × 110).

and the stratum granulosum was observed. Both can be demonstrated for the first time in 16- to 17-day-old embryos. Similar observations have been made in mouse back skin [9,20,22] and also in man, where the occurrence of Langerhans cells has been reported during the 14th to 15th embryonic week [23,24]. First signs of beginning ortho- and para-keratinization can be seen as early as the 14th to 16th weeks in utero [23–25].

In the mouse tail epidermis, postnatal day 9 is crucial insofar as the first distinct morphologic signs of the later scale-interscale pattern of tail epidermis are clearly visible. Although the granular layer is still present in the entire epidermis, Langerhans cells begin to assemble in presumptive interscale regions and to degenerate [26] in what will be scale regions. This process leads to distinct patterns of Langerhans cells and ortho- and para-keratinized zones seen in the adult mouse tail epidermis. These have also been demonstrated by assaying unspecific esterase activity [27].

Although the intimate relationship between the occurrence of Langerhans cells and the granular layer is best visible in mouse tail epidermis, there are numerous examples where similar situations are encountered. For example, the keratinized "stress regions" of oral epithelium of primates [25, 28,29] show different patterns of ortho-keratinization in that the granular layer is pronounced in the hard palate and the dorsal surface of the tongue but weak in the vestibular gingiva and absent from the crevicular gingiva [28,30]. The same order of distribution was found for high-level Langerhans cells [31]. High-level dendritic cells

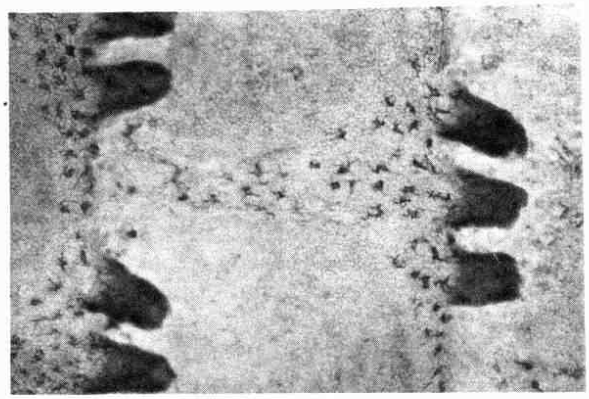

FIG. 10. Langerhans cells in EDTA-separated sheet of 7-week-old mouse tail epidermis (depilated) (ATPase staining; × 110).

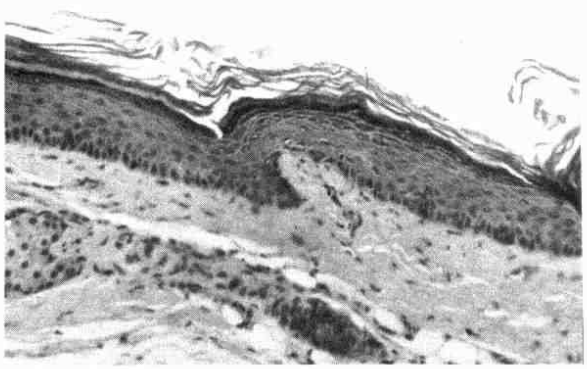

FIG. 11. Vertical section of tail skin of adult mouse skin treated with vitamin A acid for 15 days (H & E; × 120). Note the ubiquitous presence of a granular layer in the strongly hyperplastic epidermis.

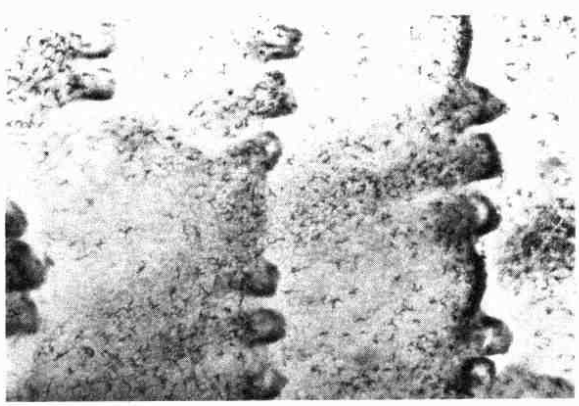

FIG. 12. Langerhans cells in EDTA-separated sheet of adult mouse tail epidermis treated with vitamin A acid for 15 days (ATPase staining; × 50). Note the presence of Langerhans cells in the scale regions.

could also be demonstrated in the fully ortho-keratinized cheek epithelium of the rat [32,33].

It has been shown that Langerhans cells are greatly reduced in human skin diseases characterized by para-keratotic differentiation, i.e., chronic psoriasis and chronic eczema [34], whereas their number is increased in disorders with augmented ortho-keratinization, i.e., lichen ruber and ichthyosis [13]. Finally, Langerhans cells have been shown to appear in the urinary bladder epithelium of vitamin A-deficient rats where normally they are absent [35]. It is known that vitamin A-deficiency results in a conversion of nonkeratinized bladder epithelium to an ortho-keratinized squamous epithelium [36]. Surprisingly also, the action of an excess of vitamin A on mouse tail epidermis leads to the appearance of Langerhans cells in the scale region and is accompanied by the formation of a pronounced granular layer.

The biologic function of Langerhans cells is still a matter of dispute. It has been proposed that they may be involved in contact allergy as well as other immunologic reactions, particularly in cell-mediated reactions to the skin [37]. It may be asked how such a concept can be reconciled with the peculiar distribution of Langerhans cells in oral epithelium of primates and in mouse tail epidermis. Furthermore, Langerhans cells have been related to the production of inhibitors of epidermal cell proliferation (chalones) [15,34] along with the suggestion that the inhibitor is produced in the Langerhans granule [15]. This would imply an inverse relationship between Langerhans cell frequency and the rate of cell proliferation as it is indeed seen in psoriatic epidermis [34,38]. On the other hand, the number of Langerhans cells is increased in ichthyosis, although the proliferative rate of keratinocytes remains unaltered [39]. Furthermore, the frequency of Langerhans cells per unit area found in the epidermis of the hairless region proximal to the mouse footpad is almost twice that found in the thinner epidermis of the mouse ear [10]. However, the epidermal proliferation rate is higher in the footpad than in the ear [40,41]. In mouse tail epidermis the labeling indices in the scale- and interscale-region epidermis are essentially comparable (unpublished results) although the scale epidermis does not contain ATPase-positive cells at all. Finally, an active inhibitor of epidermal DNA synthesis, presumably the G1 chalone, can be extracted from the epidermis of newborn chicken (S. Bertsch and F. Marks, personal communication), although Langerhans cells have not yet been demonstrated in avian epidermis [9].

Another proposal, which would be more consistent with results reported here is that Langerhans cells are involved in the process of ortho-keratinization [2,27]. In the ortho-keratinized epidermis, numerous hydrolytic enzymes are strongly if not selectively concentrated in the region of the granular layer, forming a continuous band upon appropriate histochemical staining [2,6]. These enzymes are thought to be responsible for the degradation of keratinocytes. Since similar enzymes can be demonstrated also in Langerhans cells [42], it is tempting to speculate that these cells may contribute to the autolytic processes of keratinocytes. On the other hand, it can be excluded that Langerhans cells are the only donors of the epidermal hydrolytic enzymes since these enzymes occur also in sites where Langerhans cells are completely absent or strongly reduced, i.e., tail scale epidermis or para-keratotic psoriatic epidermis [2,6]. However, in those cases the enzymes are not concentrated in a region where a granular layer should be expected but are spread more or less over the whole epidermis, the horny layer included [6].

If Langerhans cells influence the degree of keratinization in the proposed manner, their appearance should lead morphologically to the "induction" of the granular layer. It remains to be seen whether findings such as the vitamin A-induced appearance of Langerhans cells or the disappearance of Langerhans cells in the development tail scale epidermis of the mouse may provide a possible experimental starting point to resolve this question.

We are grateful to Drs. I. Mackenzie and A. Balmain for helpful advice and discussions.

REFERENCES

1. Spearman RIC: The evolution of mammalian keratinized structures, Symposium of the Zoological Society of London: The Mammalian Epidermis and Its Derivatives. Edited by GJ Ebling. London/New York, Academic, 1964, pp 55–81
2. Jarrett A, Spearman RIC: Histochemistry of the Skin—Psoriasis. London, English Universities Press, 1964
3. Spearman RIC, Garretts MB: The effect of subcutaneous saline injections on growth and keratinization of mouse tail epidermis. J Invest Dermatol 46:245–250, 1966
4. De Meijere JCH: Über die Haare der Säugethiere besonders über ihre Anordnung. Gegenbaurs Morphol Jahrb 21:312–415, 1894
5. Schweizer J, Marks F: Formation of new hair follicles in the epidermis of the mouse tail induced by the tumor-promoter 12-o-tetradecanoyl-phorbol-13-acetate. Cancer Res (in press)
6. Jarrett A, Spearman RIC, Hardy JA: The histochemistry of keratinization. Br J Dermatol 71:277–295, 1959
7. Wrenche R, Britten AZ: Evaluation of coal tar fractions for use in psoriasiform diseases using the mouse tail test. Br J Dermatol 92:575–579, 1975
8. Wolff K, Winkelmann RK: Quantitative studies on the Langerhans cell population of guinea pig epidermis. J Invest Dermatol 48:504–513, 1967
9. Reams WM, Tompkins SP: A developmental study of murine epidermal Langerhans cells. Dev Biol 31:114–123, 1973
10. Mackenzie IC, Squier CA: Cytochemical identification of ATPase-positive Langerhans cells in EDTA-separated sheets of mouse epidermis. Br J Dermatol 92:523–533, 1975
11. Giacometti L, Montagna W: Langerhans cell uptake of tritiated thymidine. Science 157:439–440, 1967
12. Schellander F, Wolff K: Zur autoradiographischen

Markierung von Langerhans Zellen mit ^{3}H-Thymidin. Arch Klin Exp Dermatol 230:140–145, 1967
13. Prunieras M: Interactions between keratinocytes and dendritic cells. J Invest Dermatol 52:1–17, 1969
14. Hashimoto K, Tarnowski WM: Some new aspects of the Langerhans cells. Arch Dermatol 97:450–464, 1968
15. Potten CS, Allen TD: A model implicating the Langerhans cell in keratinocyte proliferation control. Differentiation 5:443–447, 1976
16. Bertsch S, Marks F: Lack of an effect of tumor-promoting phorbol esters and of epidermal G1 chalone on DNA synthesis in the epidermis of newborn mice. Cancer Res 34:3283–3288, 1974
17. Scaletta LJ, MacGallum DK: A fine structural study of divalent cation mediated epithelial union with connective tissue in human oral mucosa. Am J Anat 133:431–439, 1972
18. Wachstein M, Meisel E: Histochemistry of hepatic phosphatases at a physiological pH with special reference to the demonstration of bile canaliculi. Am J Clin Pathol 27:13–19, 1957
19. Lawrence D, Bern HA: On the specificity of the response of mouse epidermal to vitamin A. J Invest Dermatol 31:313–325, 1958
20. Weiss LW, Zelickson AS: Embryology of the epidermis: ultrastructural aspects. II. Period of differentiation in the mouse with mammalian comparisons. Acta Derm Venereol (Stockh) 55:321–329, 1975
21. Jimbow K, Sato S, Kukita A: Langerhans cells in the normal human pilosebaceous system. J Invest Dermatol 52:177–180, 1969
22. Weiss LW, Zelickson AS: Embryology of the epidermis: ultrastructural aspects. III. Maturation and primary appearance of dendritic cells in the mouse with mammalian comparisons. Acta Derm Venereol (Stockh) 55:431–442, 1975
23. Breathnach AS, Wyllie LM: Electron microscopy of melanocytes and Langerhans cells in human fetal epidermis at fourteen weeks. J Invest Dermatol 44:51–60, 1965
24. Hashimoto K, Gross BG, DiBella RS, Lever WF: The ultrastructure of the skin of human embryos. IV. The epidermis. J Invest Dermatol 47:317–335, 1966
25. Adams D: Keratinization of oral epithelium. Annals of the Royal College of Surgeons of England 58:351–358, 1976
26. Potten CS, Allen TD: The fine structure and cell kinetics of mouse epidermis after wounding. J Cell Sci 17:413–447, 1975
27. Riley PA: Esterase in epidermal dendritic cells of the mouse. A study of the histochemical properties and distribution of activity of the enzyme in relation to patterning in the tail. Br J Dermatol 78:388–397, 1966
28. Squier CA, Johnson NW, Hackemann M: Structure and function of normal human oral mucosa, Oral Mucosa in Health and Disease. Edited by AE Dolby. Oxford/London/Edinburgh/Melbourne, Blackwell, 1975, pp 1–112
29. Weinmann JP, Meyer J, Medak H: Correlated differences in granular and keratinous layer in the mucosa of the mouse. J Invest Dermatol 34:423–431, 1960
30. Weinmann JP, Meyer J: Types of keratinization in human gingiva. J Invest Dermatol 32:87–94, 1959
31. Hutchens LH, Sagebiel RW, Clarke MA: Oral epithelial dendritic cells of the rhesus monkey. Histological demonstration, fine structure and quantitative distribution. J Invest Dermatol 56:325–336, 1971
32. Alvarez OF, Meyer J: Variable features and regional differences in oral epithelium, Current Concepts of the Histology of Oral Mucosa. Edited by CA Squier, J Meyer. Springfield, Ill, Thomas, 1971, pp 97–113
33. Squier CA: A study of the dendritic cells in separated sheets of oral epithelium in the rat. Arch Oral Biol 14:381–384, 1969
34. Lisi P: Investigation on Langerhans cells in pathological human epidermis. Acta Derm Venereol (Stockh) 53:425–428, 1972
35. Wong YC, Buck RC: Langerhans cells in epidermoid metaplasia. J Invest Dermatol 56:10–17, 1971
36. Hicks RM: Hyperplasia and cornification of the transitional epithelium in the vitamin A-deficient rat. Ultrastruct Res 22:206–230, 1968
37. Silberberg-Sinakin J, Thorbecke GJ, Baer RL, Rosenthal SA, Berezowsky V: Antigen-bearing Langerhans cells in skin, dermal lymphatics and in lymph nodes. Cell Immunol 25:137–151, 1976
38. Giacometti L: Cells in motion, Primate News. Med Res Found Oregon Publication, Jan 1968
39. Fisher LB, Well GC: The mitotic rate and duration in lesions of psoriasis and ichthyosis. Br J Dermatol 80:235–242, 1968
40. Christophers E, Lawrence EG: Regional variations in mouse skin. Quantitation of epidermal compartments in two different body sites. Virchows Arch [Zellpathol] 12:212–222, 1973
41. Potten CS: Epidermal transit times. Br J Dermatol 93:649–658, 1975
42. Wolff K, Winkelmann RK: Nonpigmentary enzymes of the melanocyte-Langerhans cell system, Advances in Biology of Skin, vol 8, The Pigmentary System. Edited by W Montagna, F Hu. New York, Pergamon, 1967, pp 135–167